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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/877,244	06/11/2001	James M. Staddon	0623.1090001/EKS/BJD	9543

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EXAMINER	
LANDSMAN, ROBERT S	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/877,244	STADDON ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 6-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 6-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *6/11/01* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Formal Matters

A. The Amendment dated 12/3/03 has been entered into the record.

B. Claims 1-19 were pending. However, Applicants canceled claims 4, 5 and 9-19. Therefore, claims 1-3 and 6-8 are pending and are the subject of this Office Action.

C. All Statutes not found in this Office Action can be found, cited in full, in a previous Office Action.

2. Specification

A. The objection to the specification has been withdrawn in view of Applicants' amendment to the title.

B. The objection to the specification has been withdrawn in view of Applicants' amendment to amend the phrase "p120/p120" to recite "p120/p100."

3. Claim Rejections - 35 USC § 101

A. The rejection of claims 1-3 and 6-8 under 35 USC 101 has been withdrawn in view of Applicants' removal of the phrase "the use of."

B. Claims 1-3 and 6-8 remain rejected under 35 USC 101 for the reasons already of record on page 3 of the Office Action dated 6/30/03. Applicants argue that the specification clearly states that the phosphorylation state of p120 and/or p100, and the regulation of p120/p100 serine/threonine phosphorylation via a VEGF-initiated pathway, may be important in pathologies involving cancer and hypoxia and for reducing edema (e.g. page 4, line 4-5; page 5, line 20, to page 6, line 6). Applicants also argue that the present specification clearly states that the presently claimed methods can be used as diagnostic tests useful for making therapeutic decisions or reporting on the efficacy of therapeutic drugs (page 4, lines 5-7; page 6, lines 11-15).

These arguments have been considered, but are not deemed persuasive. As noted in Applicants' arguments, and as seen in the specification, the term "may" is used repeatedly when discussing the potential function of modulating p120/p100 via a VEGF-mediated pathway. For example, the specification states that the presently claimed methods may be important in pathologies involving cancer

and for reducing edema. However, Applicants have not provided any support for these alleged utilities. "Pathologies involving cancer" could include a host of diseases, and it is not even clear that the subject would have cancer. Respectfully, this phrase is unclear to the Examiner. Applicants have not shown any link between the screening methods of the present invention and a treatment for cancer, a pathology involving cancer, or the treatment of edema. At this point, these utilities are speculative. The use of these methods for "diagnostic tests" is also not a specific or substantial utility since it is not known for what conditions/endpoints one would be testing. It is believed that all pertinent arguments have been addressed.

4. Claim Rejections - 35 USC § 112, first paragraph - enablement

A. Claims 1-3 and 6-8 remain rejected under 35 USC 112 for the reasons already of record on page 4 of the Office Action dated 6/30/03 as well as for the reasons given in the above rejection under 35 USC 101. Applicants argue that the claimed invention is enabled because it has utility as argued previously. Applicants' arguments have been fully considered, but are not found to be persuasive for the reasons discussed above.

5. Claim Rejections - 35 USC § 112, first paragraph – written description

A. Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These are genus claims. The claims recite "VEGF-initiated pathway. The specification provides a written description of only one pathway – PKC. No other species are described within the instant specification. The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus. Thus the scope of the claims includes numerous variants and the specification and claims do not provide any guidance as to what other VEGF-mediated pathways exist. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. "VEGF-initiated pathway" alone is insufficient to describe the genus. One of skill in the art would reasonable conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus at the time the invention was made.

6. Claim Rejections - 35 USC § 112, second paragraph

A. The rejection of claims 1-3 and 6-8 under 35 USC 112, second paragraph, has been withdrawn in view of Applicants' amendments to the claims to provide sufficient method steps.

7. Claim Rejections - 35 USC § 102

A. The rejection of claims 1-3 under 35 USC 102(b) as being anticipated by Esser has been withdrawn in view of the fact that Esser do not teach treating cells with both VEGF and PlGF152, as recited in the present claims.

B. The rejection of claims 1-3 under 35 USC 102(b) as being anticipated by Staddon has been withdrawn in view of the fact that Staddon do not teach treating cells with both VEGF and an agent, as recited in the present claims.

8. Claim Rejections - 35 USC § 103

A. The rejection of claims 1-3 and 6-8 under 35 USC 103(a) as being anticipated by Staddon has been withdrawn in view of Applicants' arguments that Staddon does not qualify as prior art under 35 USC 103(c).

B. Claims 1, 2, 6 and 8 are rejected under 35 USC 103(a) as being unpatentable over Esser et al. The claims recite a method of screening a substance capable of affecting the phosphorylation state of p120 and/or p100 by contacting cells with VEGF and a test agent. As can be seen in Figure 6 of Esser, VEGF was known to phosphorylate p120. In the first paragraph of the Discussion, Esser teaches that VEGF induces a strong increase in tyrosine phosphorylation of the adherens junction components VE-cadherin, l-catenin, plakoglobin, p120 and the cell-cell adhesion molecule, PECAM-I, in cultures of confluent HUVEC cells. They further teach that tyrosine phosphorylation of junctional proteins has been associated with loss of integrity of intercellular adhesions. Therefore, they conclude that, as VEGF stimulates migration and permeability, both of which involve destabilization of intercellular junctions, it appears that tyrosine phosphorylation of VE-cadherin and catenins is intimately linked to a functional change of intercellular adhesion. Though Esser do not teach a screening assay using VEGF and an agent, they do test, albeit individually, other agents. They demonstrated that PlGF152 failed to induce a significant increase in tyrosine phosphorylation of total cellular proteins and of adherens junction components. Therefore, Esser do teach a screening method. Since it was known that VEGF phosphorylation of specific

components, including p120, is important in cell adhesion, it would have been obvious for one of ordinary skill in the art at the time of the present invention to have screened compounds for their ability to alter VEGF-induced phosphorylation of adherins junction components, including p120 in order to better understand cell adhesion and factors which affect adhesion. It would have been obvious to one of ordinary skill in the art at the time of the invention to have screened compounds in the presence of VEGF in either the presence or absence of a test agent since this is how routine drug screening methods are performed. The use of a test compound in the presence of a known compound would easily allow the artisan to determine the effect of that agent on the known compound for the purposes of modulating the known compound and, therefore, its effects in the cell, such as cell adhesion.

The reference is silent with respect to the cell comprising p100. However, in absence of evidence to the contrary, it would be expected, in absence of evidence to the contrary, that cells comprising p120 would also comprise p100. It is well-known by one of ordinary skill in the art that p100 and p120 belong to a family of proteins which are localized to cellular adherin junctions. Therefore, it would be expected that, in choosing a cell with a p120, one would have chosen a cell which also contained p100. Regardless, the claimed methods do not require any function of p100, only that the cells comprise this protein.

C. Claims 1-3 and 6-8 remain rejected under 35 USC 103(a) as being unpatentable over Esser et al. in view of Ratcliffe et al. for the reasons already of record on pages 5-6 of the Office Action mailed 6/30/03. Applicants argue that Esser do not teach treating cells with both VEGF and an agent which affects the phosphorylation of p100 or p120, as recited in the present claims. Applicants argue that the that the requisite motivation for establishing a prima facie case of obviousness must be found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. Applicants argue that the Examiner's statement regarding "a screening assay using VEGF and a PKC pathway to screen for competitors and activators of VEGF" does not provide, nor rely upon, the proper motivation required to combine the cite references, nor that this statement provides any acceptable objective evidence or sound scientific reasoning that would provide such motivation. They argue, therefore, that the Examiner is using hindsight.

These arguments have been considered, but are not deemed persuasive. As discussed in paragraph B of this section, though Esser do not teach a screening assay using VEGF and an agent, they do test, albeit individually, other agents. They demonstrated that PlGF152 failed to induce a significant increase in tyrosine phosphorylation of total cellular proteins and of adherens junction components. Therefore, Esser do, in fact, teach a screening method. Therefore, it would have been obvious to one of ordinary skill

in the art at the time of the invention to have screened compounds in the presence of VEGF in either the presence or absence of a test agent since this is how routine drug screening methods are performed. The use of a test compound in the presence of a known compound would easily allow the artisan to determine the effect of that agent on the known compound for the purposes of modulating the known compound and, therefore, its effects in the cell, such as cell adhesion.

Therefore, the remaining issues are (1) the fact that the Esser is silent as to the presence of both p100 and p120 in the cells, (2) the fact that dephosphorylation occurs on serine and threonine residues and (3) the motivation to measure a PKC pathway.

Regarding the first issue, Ratcliffe do teach that p100 and p120 are localized to cellular adherin junctions. Therefore, in absence of evidence to the contrary, it would be expected that, in choosing a cell with a p120, one would have chosen a cell which also contained p100. Regardless, the claimed methods do not require any function of p100, only that the cells comprise this protein.

Regarding the second issue, dephosphorylation of serine and threonine residues on p100 and p120 would be an inherent property of p100 and p120. Therefore, the use of p100 and p120 would inherently meet the limitations of claim 3. In fact, Ratcliffe teach that "this permeability increase is accompanied by dephosphorylation of p100/p120 on serine and threonine residues.

Finally, regarding the use of PKC-p120/p100 pathway, Ratcliffe clearly teach the importance of PKC in the p120/p100 pathway (Abstract) – "Protein kinase C must act, directly or indirectly, by perturbing this phosphorylation cycle, by inhibition of a p100/p120 kinase and/or activation of a phosphatase. These data clearly show that p100 and p120 are targets of a novel protein kinase C signaling pathway. Dephosphorylation of these proteins precedes the permeability increase across epithelial cell monolayers seen in response to phorbol esters, raising the possibility that this pathway may play a role in the modulation of intercellular junctions." Therefore, the fact that VEGF was known, as taught by Esser, to modulate p120, taken with the teachings of Ratcliffe that PKC is clearly involved in the p120/p100 pathway, would have provided the artisan with sufficient motivation to have practiced the claimed invention.

9. Double Patenting

A. The provisional rejection of claims 1-3 and 6-8 under the judicially created doctrine of double patenting over all claims of copending Application No. 10/349,111 and 10/349,074 has been withdrawn in view of the fact that these applications arose from a restriction requirement.

10. Other Issues

A. Though not being published on a IDS, U.S. Patent Application 09/848,353 has been considered by the Examiner.

11. Conclusion

A. No claim is allowable.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (571) 272-0888. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached on (571) 272-0961.

Official papers filed by fax should be directed to (703) 872-9306. Fax draft or informal communications with the examiner should be directed to (571) 273-0888.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-0700.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
July 01, 2004

ROBERT LANDSMAN
PATENT EXAMINER